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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.						
10/748,637	12/30/2003	Nancy L. Brackett	7230-9	6890						
7590		03/17/2008								
Stanley A. Kim, Ph.D., Esq. Akerman Senterfitt Suite 400 222 Lakeview Avenue West Palm Beach, FL 33401-6183		<table border="1"><tr><td>EXAMINER</td></tr><tr><td>SCHUBERG, LAURA J</td></tr><tr><td>ART UNIT</td><td>PAPER NUMBER</td></tr><tr><td>1657</td><td></td></tr></table>			EXAMINER	SCHUBERG, LAURA J	ART UNIT	PAPER NUMBER	1657	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/748,637	<b>Applicant(s)</b> BRACKETT ET AL.
	<b>Examiner</b> LAURA SCHUBERG	<b>Art Unit</b> 1657

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 28 December 2007.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,3,5,6 and 8-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1,3,5,6 and 8-19 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/1449)  
 Paper No(s)/Mail Date \_\_\_\_\_
- 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_
- 5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

#### **DETAILED ACTION**

##### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/28/2007 has been entered.

Claims 1, 3, and 12-15 have been amended.

Claims 2, 4 and 7 have been canceled.

Claims 1, 3, 5, 6, and 8-19 are pending and have been examined on the merits.

##### ***Response to Arguments***

Applicant's arguments filed 12/28/2007 have been fully considered but they are not persuasive. Applicant's arguments have been addressed in so far as they relate to the new rejections below. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant argues that Alexander neither teaches nor discloses a method of increasing sperm motility and does not teach that treating the seminal plasma is helpful in treating any disease. Applicant asserts that Alexander does not even mention infertility and SCI.

This is not found persuasive because Alexander specifically states that treatment of men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in components or fractions of semen, preferably seminal plasma, comprising administering anti-cytokine agents, such as ant-TNF-alpha agents is provided by the method (column 7 lines 30-36). Although Alexander's invention has been described with regard to preferred embodiments, "it should be understood that various modifications will become apparent to those of skill in the art upon review of the present disclosure" (column 51 lines 8-11). Therefore, Alexander is clearly contemplating treating other diseases that are related to elevated levels of cytokines in seminal plasma.

Applicant argues that combining Gruschwitz with Alexander does not result in the instant invention. Applicant asserts that Gruschwitz does not mention SCI and instead teaches a correlation between cytokine content and the presence of a urogenital tract infection.

This is not found persuasive because Gruschwitz teaches a connection between patients with increased levels of TNF $\alpha$ , IL1 $\beta$ , and IL6 and reduced sperm motility (page 162 column 2 lines 17-20) and because the method of Alexander provides for treating men determined to be suffering from a disorder associated with elevated levels of one

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or more cytokines in one or more components or fractions of semen comprising administering one or more ant-cytokine agents (column 7 line 35). If these increased levels of cytokines decrease motility of sperm as suggested by Gruschwitz, then treatment addressing those increased levels would make the administration of Alexander's method an obvious choice.

Applicant argues that Angelopoulos does not cure the deficiencies of Alexander in view Gruschwitz. Applicant asserts that Angelopoulos is limited to the effects of tissue culture versus addition of pentoxifylline and 2-deoxyadenosine on non-motile sperm in testicular biopsies of azoospermic men. Applicant asserts that Angelopoulos did not study cytokines or seminal plasma or anticytokine agents and that Angelopoulos is directed to the occurrence of a non-pathological condition.

This is not found persuasive because Angelopoulos teaches that ISCI (an infertility treatment for males) benefits from enhancement of sperm motility and that there are several alternatives for accomplishing this (page 240). Angelopoulos is relevant in that male infertility in general and sperm motility specifically, can also be addressed by direct (*in vitro*) treatment of a sperm sample with agents that enhance sperm motility.

Applicant argues that Brackett does not teach or disclose that sperm may be treated with anticytokine agents to increase sperm motility

This is not found persuasive because Brackett teaches that men with SCI and leukocytospermia have cytotoxic levels of cytokines (p.1227). This teaching would qualify these disorders as suitable for anti-cytokine treatment as disclosed by

Alexander. Also, Alexander does not teach that the method is limited to systemic administration and specifically states that modifications can be made to the method, therefore Alexander does not teach away from directly treating seminal plasma.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 5, 6, 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1) in view of Gruschwitz et al (Journal of Andrology 1996), Angelopoulos et al (Fertility and Sterility 1999) and Brackett et al (Physical Therapy 1996).

Amended claim 1 is now drawn to a method comprising: a) providing from an infertile male subject having a spinal cord injury a biological sample comprising sperm and at least one cytokine selected from a group consisting of TNF $\alpha$ , IL1 $\beta$ , and IL6 ; and b) contacting the biological sample in vitro with an agent that inactivates or reduces the biological activity of the at least one cytokine under conditions that result in increased sperm motility, wherein the sperm having increased motility can be used to impregnate a female subject.

Dependent claims include wherein the male subject has leukocytospermia (claim 3), wherein the sample comprises fluid from the male reproductive tract (claim 5), wherein the sample comprises semen (claim 6), wherein the agent is an antibody that specifically binds to a receptor for the at least one cytokine (claims 8-15) and wherein the agent is a soluble cytokine receptor that specifically binds to the at least one cytokine, TNF $\alpha$ , IL1 $\beta$ , and IL6 (claims 16-19).

Alexander teaches a method that provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in

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one or more components or fractions of semen comprising administering one or more ant-cytokine agents (column 7 line 35). Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8). The use of antibodies that specifically bind to the cytokines such as TNF $\alpha$ , IL1 $\beta$ , and IL6 is taught (column 11 line 10) as well as the use of soluble cytokine receptors that bind to the cytokines TNF $\alpha$ , IL1 $\beta$ , and IL6 (column 29, US 5,770,401). Alexander also teaches that various modifications would become apparent to those of skill in the art upon review of reference's disclosure (column 51 lines 8-13).

Alexander does not specifically teach treating male infertility caused by a spinal cord injury by contacting a semen sample that contains cytokines with an agent that inactivates or reduces the activity of the cytokines. Alexander does not teach wherein the subject has a spinal cord injury or leukospermia. However, Alexander does teach that the method may be used to treat conditions associated with elevated levels of a cytokine, such as TNF $\alpha$  (column 5 line 12) and that there is a connection between leukospermia and levels of IL-6 (references cited, Shimoya et al).

Gruschwitz teaches that patients exhibiting increased levels of TNF $\alpha$ , IL1 $\beta$ , and IL6 showed a significantly reduced amount of progressively motile spermatozoa (page 162 column 2 lines 17-20). These cytokines may result in decreased sperm motility and therefore in reduced ova-penetrating properties (page 162 column 2 lines 42-47).

Angelopoulos teaches a method for enhancing sperm motility that is an alternative to applying motility stimulants for intracytoplasmic sperm injection (page 240). Angelopoulos also teaches the advantages and disadvantages of the different methods of enhancing sperm motility of a semen specimen (page 243, column 1, 2<sup>nd</sup> paragraph).

Brackett teaches that leukocytospermia is observed in many men with SCI and that this condition is thought to contribute to poor semen quality because studies indicate an association with reductions in sperm motility and loss of sperm function as a result of cytotoxic cytokines (page 1227 column 1, 2<sup>nd</sup> paragraph).

One of ordinary skill in the art would have been motivated to use the method of Alexander as a treatment for infertile males because Gruschwitz teaches a connection between patients with increased levels of TNF $\alpha$ , IL1 $\beta$ , and IL6 and reduced sperm motility (page 162 column 2 lines 17-20) and because the method of Alexander provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen comprising administering one or more anti-cytokine agents (column 7 line 35). One of ordinary skill in the art would have been motivated to use the method of Alexander directly on semen samples, such as in intracytoplasmic sperm injection (ISCI-which is a treatment for male infertility) because Angelopoulos teaches that ISCI benefits from enhancement of sperm motility and that there are several alternatives for accomplishing this (page 240). In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander)

where fertilization was to be accomplished by alternative methods that require collection of the semen sample prior to fertilization (such as ISCI). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8).

One of ordinary skill in the art would have been motivated to use the method of Alexander to treat men with SCI and leukocytospermia because Alexander teaches that the method can be used to treat conditions associated with elevated levels of a cytokine (column 5 line 12) and Brackett teaches that men with SCI and leukocytospermia have cytotoxic levels of cytokines (p.1227). In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander) where fertilization was to be accomplished by alternative methods that require collection of the semen sample prior to fertilization (such as with spinal cord injured patients). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches the use of anti-cytokine compounds for IL-6 and also that there is a connection between IL-6 and leukospermia (also known as leukocytospermia).

Therefore, the combined teachings of Alexander, Gruschwitz, Angelopoulos and Brackett render obvious Applicant's invention as claimed.

Claims 1, 3, 5, 6, 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skurkovich et al (US 5,888,511) in view of Brackett et al (Physical Therapy 1996) and Gruschwitz et al (Journal of Andrology 1996).

Skurkovich teaches a method for treating an autoimmune disease by extracorporeal (outside the body and interpreted as *in vitro*) exposure of the patient's fluid to an immunosorbent comprising autoimmune inhibitor (such as anti-IL-6 and anti-TNF antibodies as well as antibodies to TNF receptor), followed by the return of the treated fluid to the patient (column 5 lines 40-67). The term autoimmune inhibitor is used to refer to a compound which binds to or neutralizes hyperproduced cytokines (column 10 lines 55-64). Male infertility is indicated as an autoimmune disease to be treated by this method and sperm is indicated as the tissue affected (column 12, table 1).

Skurkovich does not specifically teach wherein the infertile male subject has a spinal cord injury or leukocytospermia.

Brackett teaches that leukocytospermia is observed in many men with SCI and that this condition is thought to contribute to poor semen quality because studies indicate an association with reductions in sperm motility and loss of sperm function as a result of cytotoxic cytokines (page 1227 column 1, 2<sup>nd</sup> paragraph).

Gruschwitz teaches that patients exhibiting increased levels of TNF $\alpha$ , IL1 $\beta$ , and IL6 showed a significantly reduced amount of progressively motile spermatozoa (page 162 column 2 lines 17-20). These cytokines may result in decreased sperm motility and therefore in reduced ova-penetrating properties (page 162 column 2 lines 42-47).

Therefore, one of ordinary skill in the art would have been motivated to apply the method of Skurkovich to infertile male subjects with spinal cord injuries and leukocytospermia because Brackett teaches that these subjects suffer from poor sperm quality due to cytotoxic cytokines (hyperproduced cytokines). One of ordinary skill in the art would have been motivated to use semen as the type of fluid used since this is fluid where sperm are located. One of ordinary skill in the art would have had a reasonable expectation of success because Skurkovich suggests that male infertility is a condition that can be treated and that the tissue type affected was sperm.

One of ordinary skill in the art would have been motivated to include anti-IL1 $\beta$  as well as anti-IL-6 and anti-TNF antibodies and antibodies to TNF receptor as the autoimmune inhibitors because Gruschwitz teaches that patients exhibiting increased levels of TNF $\alpha$ , IL1 $\beta$ , and IL6 showed a significantly reduced amount of progressively motile sperm. One of ordinary skill in the art would have had a reasonable expectation of success because Skurkovich teaches that additional interleukin antibodies can be used as well (column 5 lines 32-52).

Therefore the combined teachings of Skurkovich, Brackett and Gruschwitz render obvious Applicant's invention as claimed.

### ***Conclusion***

**No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford Jr/  
Primary Examiner, Art Unit 1651

Laura Schuberg